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PRINCIPAL INVESTIGATOR: Anne Germain

CONTRACTING ORGANIZATION: University of Pittsburgh
Pittsburgh, PA 15260

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14. ABSTRACT This is an updated report for the last funding period. In this period of operations, we have secured IRB and appropriate renewals. Recruitment is ongoing. There was a delay in meeting the anticipated recruitment goals in this past funding period. However, recent successes with new recruitment strategies, expanding collaborative relationships with local and regional resources for veterans will allow us to achieve and meet our targeted enrollment goals in the coming period. In addition, the randomized controlled trial is now exclusively focused on recruiting OEF/OIF returnees, and all can only be randomized to the medication arms of the study. These planned changes will also enhance recruitment in the coming period. Reportable outcomes include peer-reviewed publications, research abstracts, and research training. Archival PET data analyses are under way and will better contextualize the anticipated findings from this proposal with veterans with and without PTSD.				
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Table of Contents

	<u>Page</u>
Introduction.....	4
Body.....	4
Key Research Accomplishments.....	8
Reportable Outcomes.....	8
Conclusion.....	10
References.....	10
List of Personnel.....	11
Appendices.....	12

**PT073961: Neurobiology of Sleep and Sleep Treatments in PTSD
(NOS-STIP)**

**Revised Quarterly Technical Progress Report
Progress Period: August 11, 2009 to January 31, 2010**

I. INTRODUCTION

Posttraumatic stress disorder (PTSD) adversely affects daytime functioning and sleep. Sleep disturbances also independently contribute to poor clinical outcomes, and are often resistant to first-line PTSD interventions. Sleep-focused treatments are often required to alleviate nightmares and insomnia in PTSD patients. These observations suggest that the neurobiology of sleep is altered in PTSD, and that first-line PTSD treatments fail to normalize PTSD-related neurobiological changes during sleep. Our study aims at comparing the neurobiological correlates of REM sleep and NREM sleep relative to wakefulness in OIF/OEF returnees with and without PTSD by using state-of-the science sleep neuroimaging [¹⁸F]-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET). Returnees with PTSD then complete in an 8-week, double-blind, placebo-controlled prazosin trial, and repeat sleep and PET studies post-treatment. This will allow for investigating 1) pre-treatment neurobiological sleep predictors of sleep treatment response, and for evaluation pre- to post-treatment changes in neurobiological correlates of REM sleep and NREM sleep associated with sleep treatment response.

NOTE: Sections updated and revised since the initial submission of this report in December 2009 are indicated by a vertical line in the right margin.

II. BODY

Research accomplishments associated with each task outlined in the approved Statement of Work. The tasks and timeline initially proposed and approved in the Statement of Work are provided below. Progress and outcomes on each of the task listed are detailed for this review period.

Task 1: Recruit, screen, and randomize 40 adult male and female military veterans with Posttraumatic Stress Disorder (PTSD) and 20 OIF/ OEF returnees without PTSD from ongoing and additional public advertisement and from the VAPHS (Months 6 – 45; NCTRC).

- ***Obtaining and renewing human subject research approvals (Month 1-6; NCTRC):***

Progress: This sub-task has been completed. Since August 2009, the protocol has been modified once to include the University of Pittsburgh CTSI Research Participant Registry as a recruitment tool and upload new advertisement material.

- ***Hire and train research assistant who will be in charge of recruitment, MR, and PET scheduling (Month 1-6; NCTRC)***

Progress: This sub-task has been completed. Since the last report, personnel has changed (Mrs Rowland left our team), and a new research assistant, Julia Chasler, has been hired and trained. She is responsible for the maintenance of SOPs related to sleep studies, MR, PET scheduling aspects, as well as recruitment material. All SOPs have been completed and are monitor bi-monthly for updated and revised as necessary when new policies or directives are received from the pharmacy, PET center, MR center, or Neuroscience Clinical and Translational Research Center (NCTRC).

Of note, Dr. Eric Nofzinger is currently on entrepreneurial leave of absence from the University of Pittsburgh (October 1, 2009). However, he remains on the study as a paid external consultant, so that our team can continue to benefit from his expertise and experience. He remains accessible and available at all times to discuss procedural issues and well as data interpretation issues in ongoing data analysis projects.

- ***Develop advertisement material and disseminate information about this new sleep neuroimaging research arm and referral process to clinical staff of the VA Pittsburgh PTSD programs and local units (Months 6-42; NCTRC)***

PROGRESS: We continue to work with local media and to gather feedback from research participants to refine and improve our recruitment materials. Outreach efforts include new collaborations with the University of Pittsburgh Veterans' Office, and the Pittsburgh Veterans Leadership Program.

- ***Recruit and conduct diagnostic, physical, and sleep disorders screenings in eligible participants (Months 6-42; NCTRC)***

PROGRESS: Recruitment is ongoing. The first 6 months of recruitment have been slower than anticipated for recruitment of the original EASI study (PI: Germain; PR054093), which has hampered recruitment for the present study. The original plan was to strongly rely on recruitment efforts of the ongoing double-blind, placebo-controlled trial with prazosin, an alpha-1 antagonist shown to reduce sleep disturbances in veterans with PTSD (PI: Germain; PR054093). The original recruitment efforts were primarily conducted through the VA Pittsburgh Healthcare System (VAPHS), but because of the closure of VA recruitment in June 2009, we have reoriented recruitment efforts to public media. Therefore, recruitment was delayed relative to our original plans.

Between August and December 17 2009, we had been contacted by 11 participants in the original study, but 1 only was eligible for the presented study. The other 10 participants were either not OEF/OIF returnees, or OEF/OIF returnees on medications. Of these, 1 participants without PTSD completed all screening assessments, and completed all study procedures in January 2010.

In late December 2009, we revised and significantly altered our strategies for public advertisement for enrollment. This new strategy yielded the anticipated outcomes. Between December 28th 2009 and January 28th 2010, we received a total of 235 phone calls from military veterans interested in our research studies. Of these, 48 received information for the ongoing clinical trial and were potential participant in the present neuroimaging study. Those who were not eligible included non-OEF/OIF veterans, veterans using exclusionary medications, those who reported having sleep apnea, or declined participation in the study. Four eligible participants with PTSD have been consented and are currently completing the screening and baseline phase of the parent randomized controlled trial. These could be eligible for this neuroimaging study should they be randomized to the medication arms of the randomized controlled trial. We continue to try to recontact four additional individuals who initially appeared eligible and interested, but who have not yet been scheduled for consent and intake visit.

In summary, our latest recruitment strategies have been fruitful and show significant progress in enrollment for the current study.

- ***Randomize eligible participants with PTSD into the ongoing treatment trial (Months 6-42; NCTRC). For participants randomized to the***

medication arms (prazosin or placebo), complete screening magnetic resonance (MR) scans. (Months 6-42; UPMC MR Center)

PROGRESS: This sub-task is ongoing. As indicated above, six veterans with PTSD are currently in the screening and baseline phase of the parent randomized controlled trial, to which this current neuroimaging study is attached for the rest of the parent study. Should these participants be randomized to the medication arms of the parent randomized controlled trial, they will be enrolled in the present study.

It is important to note that the parent randomized controlled trial is scheduled for termination in March 2010, as initially anticipated and planned. For the remainder of this current project, the treatment protocol will continue as currently conducted, except that participants can now only be randomized to one of the 2 medication arms (prazosin or placebo), rather than the current 1:1 randomization to medication or behavioral treatment arms. This will greatly facilitate recruitment and flow of subjects through the present neuroimaging protocol, because 1) only OEF/OIF veterans will be enrolled in this continuing study; and 2) the randomization will be limited to the medication arms (prazosin or placebo) that are directly involved in the present study, rather than the current 1:1 randomization to medication or behavioral treatment. As such, the management of recruitment efforts and subject flow through screening and baseline research procedures will be exclusively focused on OEF/OIF veterans to be enrolled in this study. We are thus confident that the number of enrolled participants will be significantly increased over the next funding periods, and that we will meet the targeted enrollment goals over the course of the award.

Task 2: To compare the neurobiology of PTSD during REM sleep and NREM sleep relative to wakefulness in returnees with and without PTSD (Months 6-48; NCTRC and UPMC PET Center).

- ***Conduct pre-treatment (baseline) clinical, polysomnographic, and PET scan studies in participants with PTSD who elect to take part in this study (Months 6-42; NCTRC, UPMC PET Center).***

PROGRESS:

- ***Recruit age- and sex-matched returnees without PTSD (Months 9-45; NCTRC)***

PROGRESS: This sub-task is ongoing. Two male participants without PTSD have completed the protocol to date. Our recent successful recruitment efforts indicate that we can also reach OEF/OIF veterans without PTSD. We do not anticipate difficulties in recruitment and completing the protocol with this group in the coming funding period.

- ***Process MR and PET scans (Months 6-46; NCTRC and PET)***

PROGRESS: This sub-task is ongoing. Imaging data review, alignment, processing, and archiving for analysis is conducted on a timely manner.

- ***Conduct preliminary and confirmatory statistical analyses with Statistical Parametric Mapping, version 2 (SPM-2) to evaluate Group (PTSD vs. Non-PTSD) X State (Wakefulness vs. NREM; Wakefulness vs. REM sleep) differences in absolute and relative regional cerebral metabolic rate of glucose (rCMRglc; Months 36-48; NCTRC).***

PROGRESS: This sub-task is not applicable for this review period.

- **Conduct preliminary and confirmatory statistical analyses with SPM-2 to evaluate the neurobiological correlates of nightmares and insomnia during REM and NREM sleep in PTSD patients (Months 36-48).**

PROGRESS: This sub-task is not applicable for this review period.

Task 3: To identify the neurobiological changes associated with sleep treatment response during REM sleep and NREM sleep relative to wakefulness.

- **Administer and monitor treatment protocols in participants with PTSD (Months 6-45; NCTRC)**

PROGRESS: As indicated above, sub-tasks related to recruitment, randomization, and treatment have been hampered, and remain ongoing. Treatment protocols with prazosin and placebo are maintained as originally proposed. We do not anticipate problems in administering and monitoring treatments in participants with PTSD who will initiate treatment in the coming funding period.

- **Conduct and complete 8-weekly treatment sessions and weekly ratings of clinical changes, treatment adherence, and side effects (Months 6-45; NCTRC)**

PROGRESS: As indicated above, sub-tasks related to recruitment, randomization, and treatment have been hampered, and remain ongoing. Treatment protocols with prazosin and placebo are maintained as originally proposed. We do not anticipate problems in administering and monitoring treatments in participants with PTSD who will initiate treatment in the coming funding period.

- **Monitor safety and adverse events (Months 6-45; NCTRC)**

PROGRESS: As indicated above, sub-tasks related to recruitment, randomization, and treatment have been hampered, and remain ongoing. Protocols for monitoring and reporting safety and adverse events have been established, and are reviewed monthly with the study physician and team.

- **Complete post-treatment assessments by using polysomnographic studies and PET scan studies, clinician-administered and self-report scales of sleep quality and disturbances, PTSD symptom severity, depression, anxiety, and health-related quality of life in participants with PTSD who complete the treatment protocol (Months 9-45; NCTRC)**

PROGRESS: As indicated above, sub-tasks related to recruitment, randomization, and treatment have been hampered, and remain ongoing. Protocols to complete post-treatment assessments and procedures are in place.

- **Identify treatment responders and non-responders. sleep treatment response is defined as a post-treatment sleep latency < 30 minutes, and wake time after sleep onset < 30 minutes, and a sleep efficiency > 85% as determined by sleep diaries and in-home sleep studies, or a decrease in > 5 points on the Pittsburgh Sleep Quality Index; and a decrease of 50% nightmares frequency as assessed by prospective logs.**
- **Initiate and complete preliminary and confirmatory data analyses to assess pre- to post-treatment changes in rCMRglc from wakefulness to REM sleep and to NREM sleep in treatment responders vs. non-responders (to prazosin, BSI, or placebo), and post-treatment**

changes in rCMRglc in responders and non-responders to rCMRglc data acquired in healthy subjects.

PROGRESS: These sub-tasks are not applicable for this review period.

Task 4: To identify the neurobiological predictors of sleep treatment response (Months 9-48; NCTRC)

- ***Initiate and complete preliminary and confirmatory data analysis to assess baseline differences in absolute and relative rCMRglc during wakefulness, REM sleep, and NREM sleep in treatment responders and non-responders with SPM-2 (Months 36-48; NCTRC).***

PROGRESS: Data necessary to initiate this sub-task are not yet available.

Task 5. Prepare and submit research reports (NCTRC) (Months 32-48; NCTRC).

PROGRESS: This sub-task is not applicable for this review period.

III. KEY RESEARCH ACCOMPLISHMENTS

- Development and implementation of successful recruitment strategies using public media.
- Initiation of complementary archival data analysis for anticipated comparisons of the neurobiological correlates that will subsequently be used to distinguish 1) combat-exposed veterans without PTSD to healthy civilians sleepers across the sleep-wake cycle; 2) veterans with PTSD to civilians with major depression or primary insomnia (two highly comorbid conditions in PTSD) across sleep and wake states.

IV. REPORTABLE OUTCOMES

Peer-Reviewed Abstracts Submitted for Scientific Presentations at International Conferences:

- Alman J, Cashmere D, Miewald J, Nofzinger E, Buysse D, Germain A. The Relationship between Absolute Beta Power and rCMRglc in Primary Insomnia during REM Sleep. Abstract submitted for an oral presentation at the SLEEP 2010 Meeting, San Antonio, TX June 5-9, 2010.
- Cohen D, Alman J, Cashmere D, Miewald J, Germain A. Quantitative EEG analysis in REM sleep in OEF/OIF combat veterans with and without PTSD. Abstract submitted for an oral presentation at the SLEEP 2010 Meeting, San Antonio, TX June 5-9, 2010.

Invited Lectures

- Germain A. *Behavioral Treatment of Insomnia in Military Personnel and Veterans*. Workshop to be presented at the Third Hidden Casualties of War Symposium sponsored by the UWF Center for Applied Psychology and the Naval Hospital Pensacola, May 2010.
- Germain A. *PTSD: The Sleeping Beast*. Workshop to be presented at the Sleep Research Society Trainee Day, June 5 2010, San Antonio, TX.

Publications

- **Germain, A.** Parasomnias I: Nightmares. In: Morin CM & Espie C, eds. *Oxford Handbook of Sleep and Sleep Disorders*. In Press.
- Hasler BP, **Germain A.** Nightmares. In: *Adult Behavioral Sleep Medicine. Sleep Medicine Clinics*, 4(4): 507-517, 2009.
- **Germain A.** Sleep and Dreams in Posttraumatic Stress Disorder. *Frontiers in Neuroscience*, Vol.3 (3), In Press.
- **Germain A**, Zadra A. Dreams and Nightmares in PTSD. Section X: Dreaming. In: Robert Stickgold & Matt Walker, eds. *The Neuroscience of Sleep*, Elsevier, pp 316-322, 2009.

Research training activities conducted under this award:

Undergraduate training:

1. Ms. Jennifer Alman, a neuroscience and biology major at Washington and Jefferson College, completed a research internship in Dr. Germain's lab between May 2009 and August 2009. Her research project focused on assessing central (brain) arousal during REM sleep in participants enrolled in our study with Posttraumatic Stress Disorder (PTSD), in comparison to archival research subjects with Primary Insomnia (PI), good sleepers (GS), and patients with major depressive disorder. Fast-frequency quantitative EEG (qEEG) activity (sigma: 12-16 Hz; beta: 16-32Hz) during REM sleep is used as a potential indicator of central arousal. Although scans for military veterans with PTSD are not yet available, Ms. Alman is complete the background study aimed at investigating the relationships between relative regional cerebral metabolic rate of glucose (rCMRglc) during REM sleep and beta activity in healthy and clinical samples. Analyses are currently under way. This project directly relates to the present study in identifying the potential neurobiological sources of beta activity (a marker of arousal) during REM sleep in healthy and clinical samples, for future comparisons with data to be collected in the present study. The research abstract summarizing these findings has been submitted for presentation at the SLEEP 2010 meeting (provided with this submission).

2. Mr. Daniel Cohen is a 1st year medical student at the University of Pittsburgh who completed a summer research project under Dr. Germain's supervision between May and August 2009. Mr. Cohen's project aims at comparing beta activity during REM sleep in returning veterans with and without PTSD using quantitative EEG analysis. Data processing is almost complete, and analysis will be undertaken in the coming weeks. It is anticipated that a research abstract summarizing these findings will be submitted for presentation at the SLEEP 2010 meeting. As heightened arousal is a core construct of the models to be tested in the present study, evaluating whether group differences in quantitative EEG measures of central arousal may provide some preliminary findings regarding overall hyperarousal during REM sleep in veterans with PTSD compared to veterans without PTSD. The research abstract summarizing these findings has been submitted for presentation at the SLEEP 2010 meeting (provided with this submission).

3. Mr. Roger Huijon is a 1st year medical student at the University of Pittsburgh who completed a summer research project under Dr. Germain's supervision between May and August 2009. His project aimed at comparing the neurobiological correlates of REM sleep relatively to wakefulness in patients with depression and insomnia. Preliminary findings indicated a complex functional neuroanatomical profile, and supplemental analyses are underway. This project will provide unique and novel data regarding neurobiological differences and similarities in rCMRglc during REM sleep relative to wakefulness in two clinical samples: patients with major depression and

patients with insomnia. As PTSD is characterized by both high levels of comorbid depression and insomnia, this summer project will provide some additional insight into the specific and unique neurobiological correlates of REM sleep in veterans with and without PTSD.

4. Mrs. Tanisha Hill-Jarrett is a Psychology Honors Student at University of Pittsburgh who started working with Dr. Germain in August 2009 on an imaging project aimed at comparing the neurobiological correlates of NREM sleep relative to wakefulness in adults with depression or insomnia. She is currently working on data analysis and interpretation. Her honors dissertation defense is scheduled for April 5, 2010. This project directly relates to the present study in identifying the potential neurobiological differences that characterize major depression and insomnia, two frequently comorbid conditions in military veterans with PTSD. Understand how depression and insomnia differ (or are similar) from wakefulness to NREM sleep in adult civilian samples will provide a comparative background to assess how veterans with and without PTSD differ from these two samples (or are similar to) across physiological states.

V. CONCLUSION

Recruitment and research activities and procedures remain ongoing. Recruitment has accrued at a slower pace than initially anticipated, but our recent successful recruitment strategies have proven fruitful, and we are confident that we can meet our targeted recruitment goals. We continue to develop collaborative relationships with local veterans' resources at the University as well as those located at other colleges.

While preliminary results are not expected for another 12 to 15 months, we have initiated complementary work using archival imaging data collected in adults with major depression or insomnia, and healthy, civilian control subjects. These analyses and report writing are ongoing, and findings will provide a comparative background for the anticipated findings in OEF/OIF veterans with and without PTSD. This will constitute a unique set of comparisons to identify and determine the neurobiological underpinnings that differ among clinical and health samples.

Anticipated imaging data before and after treatment with prazosin or placebo will also provide novel insights in the possible mechanisms underlying sleep treatment response to inform new detection, prevention, and treatment strategies that address both nighttime and daytime symptoms of PTSD and other stress-related disorders in military personnel.

VI. REFERENCES

None applicable.

VII. APPENDICES

- Abstracts submitted for the 2010 SLEEP Meeting
- Relevant published papers

VIII. SUPPORTING DATA

None to provide at this time.

List of personnel receiving pay from the research effort:

NAME (role) Equivalent	% effort	Full-Time
GERMAIN, ANNE (PI)	20.00%	1
Eric Nofzinger (Paid External Consultant)	5.00%	1
MAMMEN, OOMMEN (Co-I, study MD)	10.00%	1
PHILLIPS, MARY (Co-I)	5.00%	1
RODE,NOELLE MARIE (Data Manager)	20.00%	0.5
CHASLER, JULIA (Data entry clerk)	50.00%	1
STOCKER,RYAN (Study Coordinator)	25.00%	1
WOOD,ANNETTE MARIE (PET data manager)	10.00%	1

The Relationship between Absolute Beta Power and rCMRglc in Primary Insomnia during REM Sleep

Jennifer Alman, David Cashmere, Jean Miewald, Eric Nofzinger, M.D., Dan Buysse, M.D., and Anne Germain, Ph.D.

Introduction: Primary (PI) insomnia is characterized by increased arousal and poor sleep. However, the neurobiological correlates of PI during REM sleep have been scarcely studied. We explored the relationship between whole-night absolute beta power during REM sleep and relative regional cerebral metabolic rate of glucose (rCMRglc) in adults with PI.

Methods: 10 PI subjects (M age= 37.86 ± 9.38 years) were included in this analysis. All were medication-free and completed 3 nights of polysomnographic recordings, and [^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography scans during REM sleep. Regression analyses were conducted to evaluate the correlations between whole-night REM sleep absolute power spectral values for beta2 activity (16-32 Hz) and rCMRglc.

Results: No significant positive correlation between beta activity and rCMRglc during REM sleep was observed. Significant negative correlations between beta activity and rCMRglc during REM sleep were observed in three brain areas. The first area (x, y, z coordinates: -10, 48, 10, $Z = 3.36$, $p=0.03$) included the left inferior and middle frontal gyri and extended into cingulate gyrus. The largest area (x, y, z coordinates: 52, -66, 14, $Z = 4.15$, $p < .001$) encompassed the right inferior, middle, and superior temporal gyri and the fusiform gyrus, parahippocampal gyrus and hippocampus. Bilaterally, it also included the posterior cingulate, precuneus, superior parietal lobule. The last area (x, y, z coordinates: -34, -44, -20, $Z = 4.38$, $p = .04$) included the left fusiform gyrus, superior, inferior, and middle temporal gyri.

Conclusion: In adults with PI, decreased whole-night beta activity was associated with increased rCMRglc during REM sleep in bilaterally in temporal and parietal cortices, and in left frontal regions. Posterior brain regions have been related to quiet, resting states. Replication of these preliminary results in large samples is required.

Support:

This research was supported by the National Institutes of Health (MH053035; MH024652; MH66227; RR024153) and the Department of Defense (PT073961-W81XWH-07-PTSD-IIRA).

Abstract:

Title: Quantitative EEG analysis in REM sleep in OEF/OIF combat veterans with and without PTSD.

Authors: Daniel Cohen, Jennie Alman, David Cashmere, Jean Miewald, Anne Germain

Introduction

REM sleep disturbances have been associated with Posttraumatic Stress Disorder (PTSD), but PSG studies have yielded inconsistent findings. In this study, we used quantitative EEG (qEEG) to compare beta activity (16-32Hz) as a measure of central arousal during REM sleep in combat-exposed veterans with and without PTSD. We hypothesized that PTSD would be associated with greater beta activity.

Methods:

Participants were combat veterans of Operations Enduring/Iraqi Freedom (OEF/OIF) drawn from an ongoing clinical trial. Assessments included 2 PSG nights, and questionnaires on sleep quality and psychiatric symptoms. Participants using psychotropic medications were excluded from this analysis. The second PSG night was used for qEEG analysis. Artifacts were rejected in 4-second epochs using an automated algorithm for EMG-twitches, and manually to remove eye-movement and pulse artifacts. Artifact-free REM epochs were subjected to spectral analysis using a fast Fourier transform model. T-tests were used to compare groups. Spearman correlations were performed between beta activity and clinical variables.

Results:

No group differences were observed on PSG measures. The number of 4-second REM epochs rejected for qEEG analysis did not differ between groups. The PTSD group showed lower beta activity in REM sleep than the non-PTSD-group (mean (SD): 0.060 (0.02) vs. 0.096 (0.03), $p=0.013$). No differences were observed in other qEEG activity bands. In the combined sample, REM beta activity was negatively correlated to PTSD symptom severity ($\rho=-0.52$, $p=0.04$), PTSD avoidance symptoms ($\rho=-0.57$, $p=0.02$), but not to hyperarousal symptoms ($\rho=-0.09$, $p=0.75$).

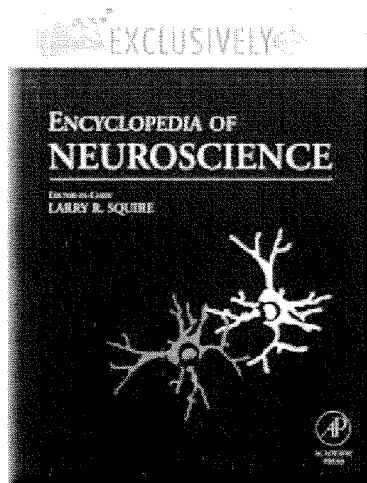
Discussion:

Contrary to our hypothesis, beta activity was lower during REM sleep in combat veterans with PTSD compared to those without PTSD, and was not related to hyperarousal symptom severity. This small study raises the possibility of a complex, non-linear link between central hyperarousal, REM sleep, and PTSD symptom severity.

Research supported by: This research was supported by the National Institutes of Health (MH053035; MH024652; MH66227; RR024153; R21MH083035-01) and the Department of Defense (PR054093-W81XWH-07-PTSD-IIRA and PT073961-W81XWH-07-PTSD-IIRA).

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Germain A and Zadra A (2009) Dreams and Nightmares in PTSD. In: Squire LR (ed.) *Encyclopedia of Neuroscience*, volume 3, pp. 655-661. Oxford: Academic Press.

Dreams and Nightmares in PTSD

A Germain, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

A Zadra, Université de Montréal, Montréal, QC, Canada

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Clinical Significance of Nightmares in Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) refers to symptoms of reexperiencing, avoidance, and hyperarousal that persist for more than 1 month after exposure to a traumatic event. Violent crimes, including rape, physical assaults, and combat exposure, constitute traumatic events that involve threat to integrity of the self or to others and are accompanied by intense fear, helplessness, or horror. Epidemiological studies indicate that community prevalence estimates of PTSD are in the range of 1–10%, with higher estimates reported for victims of interpersonal violence (20–30%) and combat veterans (15–30%). Recommended first-line treatments of PTSD include selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral interventions such as prolonged exposure and cognitive restructuring.

Nightmares are a core feature of PTSD. As many as 90% of trauma-exposed individuals who develop PTSD report disturbing dreams that bear varying degrees of resemblance to the actual traumatic event. Growing evidence suggests that trauma-related nightmares may directly contribute to the pathophysiology of PTSD. The persistence of nightmares and sleep disruption 1 month posttrauma increases the likelihood of developing PTSD at follow-up assessments. Moreover, a personal history of nightmares prior to trauma exposure can predict the severity of PTSD and other posttraumatic psychiatric symptoms. Frequent recurrent nightmares about a traumatic event can persist for years and even decades after the trauma. Trauma-related nightmares disrupt sleep and independently contribute to increased severity of daytime PTSD symptoms and increased alcohol use in trauma survivors, and adversely affect quality of life and perceived physical health.

Nightmares and Sleep following Trauma Exposure and in Chronic PTSD

In healthy persons, elaborate dream recall is more prominent following awakening from rapid eye movement (REM) sleep than from awakening from non-REM (NREM) sleep. In trauma-exposed adults, two preliminary studies suggest that disruption of

REM sleep, as indicated by increased sleep stage transitions and arousal, as well as increased sympathovagal tone during REM sleep are associated with increased PTSD symptom severity and may increase the likelihood of developing PTSD at follow-up assessments. Thus, REM sleep disruption and increased arousal during REM sleep may increase one's vulnerability to experience vivid nightmares following trauma exposure and to develop PTSD.

REM sleep disturbances have been most consistently reported in patients suffering from chronic PTSD, but other sleep alterations, such as reduction in slow-wave sleep, have also been documented. More general sleep disturbances, such as increased sleep latency, total sleep time, and duration of and number of nocturnal awakenings, have been reported in some, but not all, studies. Polysomnographic studies based on refined objective measures of central and peripheral physiological arousal, such as quantitative electroencephalography and quantitative electrocardiography, have observed indices of heightened central and peripheral arousal during sleep in patients suffering from PTSD. PTSD in patients who report trauma-related nightmares show increased duration of wakefulness after sleep onset in comparison to those who report non-trauma-related nightmares. However, REM sleep parameters, or more global sleep measures, do not correlate with specific aspects of nightmare content. These observations suggest that in chronic PTSD, trauma-related nightmares may represent expressions of a more global sleep disturbance related to heightened arousal.

Dream Recall and Nightmare-Related PTSD

Studies on dream recall frequency following trauma exposure have yielded inconsistent results. Increases in dream recall frequency following a traumatic event have been reported and the hypothesis put forth is that dream recall is facilitated by the intensity, affective charge, and references to the victims' trauma depicted in their dreams. Conversely, significant decreases in dream recall have also been documented. These data, however, are largely based on retrospective assessments conducted many months or even several years following trauma exposure. It is possible that dream recall increases immediately following an individual's exposure to trauma and subsequently diminishes over time. One comparison of high-functioning Holocaust survivors, average-functioning Holocaust survivors, and controls found that the high-functioning survivors reported fewer dreams from REM sleep (33.7%), compared to the average-functioning survivors (50.5%)

and controls (80.8%). A reduction in dream recall may thus reflect improved posttrauma adaptation in this population.

Repetition of Trauma in Dreams

The recall of dreams that replicate the traumatic event experienced by trauma victims has been described in many populations, including war veterans, adults and children exposed to war, witnesses of violence and abuse, burn victims, and individuals exposed to natural disasters. A classification system for trauma-related dreams has been put forth. Posttraumatic dreams refer to the replication of the traumatic event during sleep or the introduction of the encapsulated memory of the trauma during sleep. Modified dreams present distorted themes, elements, or emotions from the trauma. Finally, disguised dreams represent the traumatic event symbolically or metaphorically. These categories form a continuum of replication (according to the extent to which the traumatic event is represented in the dream) and of repetition (i.e., the dream's recurrence). Empirical studies support this classification system. For example, in one study of Vietnam War veterans, 304 of 316 veterans reported combat-related nightmares. An examination of their dream narratives revealed that over half of the veterans reported realistic combat dreams, 21% reported plausible war sequences that they nevertheless had not experienced, and 26% reported dreams that alluded to the war, but also included fantastical and everyday elements. In addition, a laboratory study of war veterans found that only 21% of dreams exactly replicated the traumatic event, while the majority contained distortions related to the traumatic event. Similarly, one study of patients hospitalized following an accident or assault found that 46% of reported dreams replicated the traumatic event, 33% were dissimilar to the traumatic event while containing high levels of distress, and 19% showed little similarity to the trauma or distress.

Taken together, the results reveal changes in dream content with the passage of time and with improvement in the posttrauma reaction. Dreams recalled during the initial posttrauma phase tend to include some type of repetition of the trauma while subsequent phases are characterized by more symbolic representations of the trauma and greater integration of the individual's everyday life in recalled dream content.

Trauma and Dream Content

Several studies have reported salient alterations in the content of trauma victims' dreams. Some data suggest that when compared to the dream reports from controls, dreams recalled by trauma victims tend

to be more ordinary and realistic and less salient, bizarre, and imaginative. The 'ordinary' quality of trauma victims' dreams may reflect an alteration in the process of dream construction or may be related to a protective mechanism which keeps traumatic images from intruding into everyday dreams.

Intense emotions have been documented in several studies of trauma victims' dreams. Feelings of horror, anxiety, rage, sadness, and frustration are among the most frequently reported. PTSD patients rate their nightmares as being significantly more distressing than do non-PTSD patients. Emotional preoccupations prior to bedtime may also play a role in the affective content experienced during subsequent sleep. The finding that one's mood prior to sleep is inversely related to positively or negatively experienced dream affect supports the idea that dreams may help regulate emotional equilibrium in traumatized individuals.

Some research has been directed at delineating relationships between measures of dream content and specific types of traumas.

Victims of Physical and Sexual Abuse

Themes of attack, pursuit, and of one's own death are more frequently found in the dreams recalled by victims of sexual abuse than in those recalled by control participants. Episodes of verbal and physical abuse are more evident in the dreams of physically abused women when compared to the dreams of controls. Although themes of violence and aggression often characterize women's nightmares, the nightmares reported by victims of sexual abuse are more likely to include unique themes of blood and dismemberment as well as a higher occurrence of male strangers. In addition, the dreams and nightmares of sexually abused women contain more frequent references to negative sexual activity, including themes concerning lack of trust and shame, guilt, jealousy, anger, and violence. These dreams often depict situations wherein elements of sex and aggression are confounded, in which sexuality is unpredictable and often results in fear. Victims of sexual abuse also frequently report the presence of serpents and worms in their dreams as well as references to both sexual and nonsexual body parts.

Victims of War and Violence

Exposure to an environment of war or violence is associated with dreams containing high proportions of aggressive and hostile human interactions. Themes involving immediate dangers to one's life appear more frequently in the dreams of Holocaust survivors, children that have been kidnapped, and children involved in car accidents than in nontrauma populations. It is not unusual for war veterans to report that their

traumatic dreams entail being killed in the place of their compatriots. A study of war-exposed Palestinian children found that traumatized children had more dreams with threatening strangers. Their dreams were often composed of attacks, anxiety, persecution, hostility, and nondesirable endings. In addition, nontraumatized children report more dreams of school and of their peers than do traumatized children.

That said, conflicting results exist regarding the impact of trauma and PTSD on dream content. For example, in addition to having more dreams with threatening strangers, victims of violence also report more dreams referring to their family, house, affiliations, and human connections than do controls.

Frequency of Dream-Related Disorders

Dream-related disorders, such as posttraumatic dreams, nightmares, bad dreams, and recurrent dreams, are the most frequently reported and most persistent symptoms exhibited by trauma victims. Several factors appear to mediate this association. First, a positive relationship exists between the degree and severity of trauma exposure and the frequency of dream-related disorders. Second, the victim's psychological reaction to trauma (e.g., level of anxiety) positively influences the occurrence of nightmares and other dysphoric dream experiences. Third, the time elapsed since trauma exposure appears to play an important role, with reductions in dream-related disorders occurring over time. However, it should be noted that dream disturbances can nevertheless persist for many years following the trauma.

Functional Hypotheses of PTSD-Related Nightmares

Many contemporary dream theorists suggest that dreaming is functionally significant and may subserve a biologically important function, but some argue that dreams are epiphenomenal to neurophysiological activity during REM sleep and have no value in and of themselves. While this overarching question on the function of dreaming is of phenomenological interest, the resolution of this debate is of little clinical relevance for chronic, frequent, and distressing nightmares in PTSD patients. However, understanding the possible role(s) of nightmares as one of the normal initial reactions to trauma exposure, which may also become a perpetuating condition contributing to maladaptive, chronic trauma response, has direct clinical implications regarding the development and refinement of effective nightmare-specific treatments. The following sections describe the main hypotheses put forth to explain the possible dual role of nightmares occurring posttrauma.

Nightmares and Emotional Adaptation to Trauma

Several neuropsychophysiological hypotheses of the function of dreaming have been adapted to explain the occurrence of nightmares after exposure to a trauma or other significant life events, and the role of nightmares in the pathogenesis and maintenance of PTSD. Freud proposed that nightmares reflect attempts to master anxiety and guilt associated with a traumatic experience, and to integrate traumatic experiences into one's psyche during sleep. Contemporary hypotheses are based on a similar premise – that dreaming serves a function of emotional adaptation to emotionally salient or traumatic events – and combine empirical observations supporting the role of REM sleep (and by association, dreaming) in learning, memory consolidation, emotional processing, and adaptation to stress. Given that REM sleep is associated with muscle atonia, and given the lack of detectable physiological activation during REM sleep episodes preceding awakening from nightmares, dreaming and REM sleep may provide a unique psychophysiological milieu during which traumatic memories can be reexperienced in the absence of physiological arousal. This process could facilitate the attenuation of emotional and physiological responses associated with these memories, leading to desensitization to the trauma-related memories, including a reduction of nightmares. Prospective dream collection studies in combination with repeated objective assessment of sleep patterns and other physiological parameters of central and peripheral arousal in people at high risk for trauma exposure (e.g., disaster workers, police officers, firefighters, deployed military personnel) are necessary to assess the role of nightmares in the recovery of trauma response and PTSD.

Stickgold proposed an explicit REM sleep model of the neurobiological substrates potentially subserving emotional processing and integration of trauma-related memories. Specifically, it is suggested that REM sleep provides a unique neurochemical and neurobiological brain state that allows the transfer of hippocampally mediated episodic traumatic memories and amygdala-dependent salient affect into cortically distributed semantic networks. It should be noted that the possibility has not been evaluated that PTSD-related nightmares may also reflect the failure of compensatory mechanisms aimed at preserving processes such as emotional adaptation, memory consolidation, and sleep continuity.

Sensitization Hypothesis of PTSD Nightmares

While the adaptation process may be successful in individuals who recover from trauma exposure, the persistence of nightmares in those who develop PTSD may, instead, reflect a failure of dreaming and REM

sleep to fulfill their role of emotional adaptation and memory integration. In this perspective, nightmares are the outcome of unsuccessful processing during dreaming and REM sleep. In addition, nightmares may directly contribute to the failure of the adaptation and integration process by promoting sensitization (rather than desensitization) to trauma-related memories. PTSD-related nightmares are often associated with awakenings and are accompanied by intense emotional and physiological arousal. Trauma-related nightmare content, sleep disruption induced by awakening from a nightmare, and heightened physiological and emotional arousal levels that follow such awakenings may contribute to reinforce the occurrence of nightmares and related distress during both wakefulness and sleep. In other words, the recall of nightmares can expose patients to their prior trauma and may even induce retraumatization, since PTSD nightmares often repeat a traumatic situation in whole or in part, whereas habituation to physiological arousal elicited by these memories does not occur.

There is evidence that frequent and distressing PTSD-related nightmares are associated with increased severity of daytime reexperiencing, arousal, and avoidance PTSD symptoms. Alternatively, some PTSD patients who show clinically significant improvements in PTSD following exposure-based therapy also report improvements in trauma-related nightmares, suggesting that habituation to trauma memories during wakefulness can also attenuate nightmare frequency, intensity, and related distress. Desensitization therapy has also been used successfully for the treatment of trauma-related nightmares. These observations support the hypothesis that chronic nightmares without physiological habituation may indeed contribute to the maintenance of PTSD by sensitizing patients to trauma memories.

Potential Psychophysiological and Neurobiological Underpinnings of PTSD-Related Nightmares

While several polysomnographic studies have been conducted in PTSD samples, these sleep measurement methods do not allow the identification of neurobiological underpinnings of trauma-related nightmares or, more generally, of PTSD during sleep. Such an endeavor requires the use of functional sleep neuroimaging approaches. Sleep neuroimaging has not yet been conducted in PTSD patients. However, animal models of the effects of fear conditioning on sleep, and neuroimaging sleep studies in humans, have provided valuable insights into the potential neurobiological underpinnings of altered REM and NREM sleep mechanisms following stress exposure PTSD,

and into the neurobiology of normal sleep, respectively. While animal models and sleep imaging in healthy persons limit possible extrapolation of neurobiological underpinnings of trauma-related nightmares, findings derived from these two distinct fields provide evidence for functionally significant overlaps between the neurobiology of fear and sleep regulation.

Functional neuroimaging studies conducted during wakefulness in PTSD patients are consistent with animal models of fear conditioning. PTSD is associated with hyperresponsiveness of the amygdala to threat-related stimuli, and/or a with blunted response of medial prefrontal cortical regions, which exert inhibitory control over the amygdala. Other functional findings include increased thalamic activity with trauma-related stimuli in PTSD compared to non-PTSD subjects, and hyperresponsiveness of the noradrenergic system. Of note, neuronal activity in these structures cannot be captured by conventional sleep measurement methods, which further reinforces the need to use state-of-the-science sleep neuroimaging methods in patients with PTSD.

In rodents, cued fear conditioning increases REM sleep latency, decreases REM sleep duration and number of REM bouts, and increases pontogeniculoccipital (PGO) waves, a marker of alerting mechanisms during sleep and wakefulness analogous to REMs in humans. The effects of fear conditioning on REM sleep in rodents are mediated by amygdalar projections to brain stem regions involved in alerting response and REM sleep generation. Anatomically, the interconnections that the amygdala shares with the basal forebrain, hypothalamus, preoptic area of the anterior hypothalamus, brain stem reticular formation, and solitary tract nucleus allow the amygdala to influence both wakefulness-promoting and sleep-promoting areas. Neuronal firing of the amygdala varies across the sleep-wake cycle, and stimulation of the amygdala during REM sleep increases PGO waves in REM and NREM sleep, whereas inactivation of the amygdala with tetrodotoxin decreases sleep latency and increases slow-wave activity during wakefulness, REM sleep, and NREM sleep. Conversely, ablation of the amygdala in rhesus monkeys is associated with increased sleep consolidation and total sleep time. These findings indicate that the amygdala is an important modulator of sleep and wakefulness regulation mechanisms.

Sleep neuroimaging studies conducted in healthy persons have reliably shown that REM sleep is a natural activator of the amygdala and anterior paralimbic areas and of the medial pons and thalamus. REM sleep is also associated with relative deactivation of lateral prefrontal parietal regions and primary sensory cortices. These selective activation and deactivation

patterns during REM sleep relative to wakefulness have yielded the hypothesis that dreams may reflect the mental representations of high limbic activations in conjunction with deactivation of high-order cortical regions. NREM sleep is a natural deactivator of arousal-promoting structures.

The functionally significant interconnections between the amygdala and wakefulness- and sleep-promoting areas, the unique limbic activation and cortical deactivation patterns observed during sleep in healthy persons, and the functional neuroanatomical findings in PTSD patients during wakefulness all support a role for a heightened amygdalar activity during sleep in PTSD, and provide preliminary guidance for the investigation of the neurobiology of PTSD during REM and NREM sleep. While the relationship between heightened amygdalar activity and dream content cannot yet be ascertained, the role of the amygdala in acquisition of the fear response and the emotional salience of stimuli raises the possibility that heightened amygdalar activity during REM sleep also contributes to salient, negative aspects of dreams and nightmares.

Treatments of PTSD-Related Nightmares

Nightmares are closely related to sleep disturbances, including increased sleep latency, decreased total sleep time, and increased number and duration of awakenings after sleep onset and restless or fitful sleep. Nightmares often produce an insomnia-like pattern of sleep disturbance, if not outright insomnia. Sleep avoidance and fear of darkness, frequent features associated with PTSD-related nightmares, can further reinforce the maintenance of both nightmares and insomnia.

Recommended (by the Expert Consensus Guideline Series on the treatment of PTSD) first-line treatments include Food and Drug Administration (FDA)-approved SSRIs such as sertraline and paroxetine, and cognitive-behavioral interventions such as prolonged exposure and cognitive therapy. However, nightmares are often resistant to such first-line PTSD treatments, and adjunctive treatments are often required to alleviate PTSD-related nightmares.

Several psychological and pharmacological nightmare-focused treatments have been shown to effectively reduce and eliminate nightmares in PTSD patients. Successfully treated nightmare patients often report improvements in sleep quality, feeling more rested upon awakening and having more daytime energy, and reduction in nightmares is a significant predictor of sleep improvement. In addition, nightmare reduction is associated with marked improvements in daytime PTSD symptoms, quality of life, depression and anxiety symptoms, and overall functioning. These findings suggest that at least in some cases,

chronic nightmares may represent a primary sleep disorder rather than a symptom of a psychiatric disorder, and as such can benefit from targeted, adjunctive cognitive-behavioral or pharmacological treatments.

Imagery Rescripting and Rehearsal

Numerous techniques have been proposed to treat PTSD-related nightmares, including hypnosis, lucid dreaming, eye movement desensitization and reprocessing, desensitization, and imagery rescripting and rehearsal (IRR). However, only desensitization and IRR have been the objects of controlled studies. Only IRR has been shown to effectively reduce nightmare frequency and nightmare-related distress in patients suffering from idiopathic, recurrent, or PTSD-related nightmares.

IRR for nightmares is composed of two general elements, each of which utilizes several steps in the therapeutic process. The first component is an educational/cognitive restructuring element, focused on helping nightmare sufferers to consider their disturbing dreams as a learned behavior. The second component is an imagery education/training element, which teaches nightmare patients about the nature of human imagery and how to implement a specific set of imagery steps to decrease nightmares. Generally, patients are shown how a nightmare can be effectively treated as a problem in and of itself, without any discussion or emphasis on prior traumatic events or nonsleep-related PTSD symptoms. As such, IRR seeks to minimize the use of exposure therapy as an ingredient in its procedures.

When learning IRR, patients are instructed to modify an original nightmare in any manner of their preference, and to create a new dream scenario. The new dream scenario is then rehearsed in session, and practiced each day until the next session. The rationale is that the rescripting and rehearsal of new dream imagery during the day can replace or alter nightmare scenarios experienced during sleep. Generally, patients report reductions in nightmare frequency and intensity within 6–12 weeks, and improvements are maintained for as long as 30 months.

Several variations of IRR have now been described. The distinguishing features between variations of IRR generally revolve around the degree of exposure used during treatment sessions and/or the specific application of the technique during the sessions. IRR can be delivered in group or individual formats. The number of sessions required for IRR can vary from one to six sessions. Since IRR involves minimal exposure and abreaction, its effectiveness is most likely related to the patient's ability to increase mastery over distressing dream elements by generating new dreams. Research on the scripting of new dreams linked to IRR indicates that mastery is in fact a key

ingredient in this treatment. The observed increase in mastery is all the more remarkable given that IRR does not include instructions to increase mastery when the technique is described during treatment. Although these data are consistent with the view that a dysfunctional imagery system is involved in traumatic nightmares, more work is required to elucidate the relationship between variables related to patient characteristics (e.g., traumatized vs. nontraumatized, presence of psychiatric and sleep disorders, dispositional factors, degree of distress), nightmare content and type (e.g., replicative, recurrent, lifelong, idiopathic), and therapeutic effects (e.g., enhanced self-efficacy, perceived control, modes of emotion expression and representation).

Prazosin

Prazosin is a central α_1 adrenoreceptor blocker that is FDA-approved for the treatment of hypertension. Prazosin is currently the most efficacious treatment for PTSD-related nightmares in military veterans and civilian populations with PTSD. Promising results for the use of prazosin to reduce PTSD-related nightmares became available after the Expert Consensus Guideline Series on the treatment of PTSD were established. Results from controlled trials indicate that prazosin effectively reduces chronic PTSD-related nightmares in military and civilian sample groups with PTSD. Reduction in nightmares with prazosin is associated with clinically meaningful improvements in sleep quality, overall PTSD severity, and daytime functioning in combat veterans with chronic PTSD. Most patients experience a recurrence of insomnia and nightmares upon prazosin discontinuation. The drug is well tolerated by patients, is associated with minimal side effects, and no adverse events have been reported with long-term use.

Serotonin-Potentiating Drugs

Randomized controlled trials on the efficacy of FDA-approved SSRIs for the treatment of PTSD (i.e., sertraline and paroxetine) either did not measure improvements in sleep using validated measures, or reported minimal improvements in nightmares or overall sleep quality. In fact, some SSRIs may increase the number of arousals during sleep and decrease total sleep time. Open-label trials with fluvoxamine suggest moderate improvements in PTSD-related nightmares, but randomized controlled trials have not been conducted and side effects may impede tolerability. Open-label trials and case reports suggest that serotonin-potentiating non-SSRIs, such as nefazodone and trazodone, can be associated with reductions in PTSD-related nightmares and sleep disruption. However, double-blind randomized controlled trials

in PTSD samples are not available. The need for rigorous randomized controlled trials is highlighted by the example of cyproheptadine. Initial case series suggested that cyproheptadine was a potent agent for the alleviation of PTSD-related nightmares. However, a subsequent double-blind, randomized controlled trial in Vietnam veterans with PTSD found that cyproheptadine could in fact exacerbate nightmares and sleep disruption. A few randomized controlled trials have evaluated the efficacy of monoamine oxidase inhibitors and tricyclic antidepressants for PTSD, and slight to moderate improvements were reported in some, but not all, studies. Optimal doses, durability of therapeutic gains, side effect profiles, and tolerability have not been assessed specifically for PTSD-related nightmares and sleep disruption with non-SSRIs, monoamine oxidase inhibitors, or tricyclic antidepressants. It should be noted that very few trials targeting clinically meaningful reductions in PTSD-related nightmares and sleep disturbances have used specific nightmare measures (e.g., questionnaires, sleep or dream logs) as primary outcome measures. Such measures are necessary to determine the effects of targeted treatments on specific aspects of nightmares, such as frequency, intensity, nightmare-induced sleep disruption, and associated distress.

Other Pharmacological Agents

Several medications that have sedative properties have been used in PTSD patients. Antipsychotics such as olanzapine and quetiapine have been tested in PTSD and have been associated with mixed findings as to their potential for reducing PTSD-related nightmares and insomnia. Despite the lack of evidence for their efficacy in reducing both daytime and nighttime PTSD symptoms, benzodiazepines are often prescribed to patients with PTSD. An open trial with zolpidem, a nonbenzodiazepine hypnotic, reported improvements in sleep and some improvements in nightmares in military veterans with PTSD. Case series reports on other pharmacological agents, such as topiramate, respridone, and gabapentin, among others, are also available. While most cases report some degree of improvement in nightmares and insomnia in PTSD patients, proper randomized controlled trials are necessary to fully assess the efficacy of these agents as adjunctive PTSD treatments for nightmares and insomnia, and to determine associated health risks in light of side effects such as tolerance, weight gain, and glucose dysregulation.

See also: Amygdala: Contributions to Fear; Dream Function; Dreams and Dreaming: Incorporation of Waking Events; Dreams, Dreaming Theories and Correlates of Nightmares; Nightmares; Posttraumatic Stress Disorder: Overview; Posttraumatic Stress Disorder as an

Emotional Disorder; Sleep Mentation in REM and NREM: A Neurocognitive Perspective; Sleep and Sleep States: Phylogeny and Ontogeny; Sleep and Sleep States: PET Activation Patterns; The AIM Model of Dreaming, Sleeping, and Waking Consciousness.

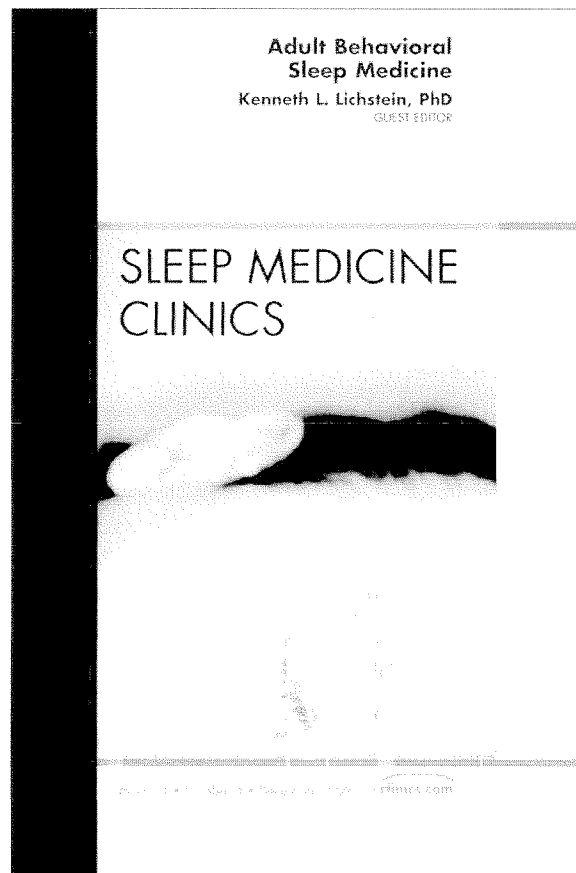
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Relevant Websites

- <http://www.aasmnet.org> – American Academy of Sleep Medicine.
- <http://www.istss.org> – International Society for Traumatic Stress Studies.
- <http://www.ncptsd.org> – National Center for PTSD (US Department of Veterans Affairs).

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Correlates and Treatments of Nightmares in Adults

Brant P. Hasler, PhD^a, Anne Germain, PhD^{b,*}

KEYWORDS

- Nightmares • Sleep • Posttraumatic stress disorder
- Pharmacology • Cognitive-behavioral treatments

This article presents the definition of nightmares and diagnostic features, followed by a discussion on the prevalence and frequency of nightmares and related methodological issues. The potential etiologic factors of nightmares, associated features, and available pharmacologic and cognitive-behavioral treatment strategies are reviewed.

Current diagnostic classifications define nightmares as frightening dreams that awaken the sleeper. However, fear is not the only emotion reported in nightmares; and the importance of the awakening criterion for functional and sleep impairments associated with nightmares has been debated in the literature. These points are briefly summarized here. In this article, the term *nightmare* is broadly used to refer to disturbed dreaming that may or may not be accompanied by an awakening, and that is associated with clinically meaningful levels of daytime distress, functional impairments, or sleep disruption.

In reviewing available data on nightmare prevalence and frequency estimates, the need for more unified methodological approaches and longitudinal designs in future studies is highlighted. Although the literature is limited on the etiology of nightmares that occur outside the context of stress or traumatic responses, this article presents hypotheses previously suggested on the correlates and potential underlying mechanisms of nightmares. Selected associated features of

nightmares (ie, psychopathology and sleep disturbances) are presented, and available and promising treatment strategies are described. Some pharmacologic and cognitive-behavioral treatments of nightmares have been shown to effectively reduce and eliminate nightmares, but few rigorous, randomized controlled clinical trials have been conducted. Finally, future directions for methodological consideration, research investigations, and clinical practice are offered.

DEFINITION

The Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR)¹ and the International Classification of Sleep Disorders, second edition (ICSD-II)² converge on defining nightmares as “intensely disturbing dreams that awaken the dreamer to a fully conscious state and generally occur in the latter half of the sleep period.” However, these diagnostic classifications also differ on 2 key points. Firstly, they differ on whether nightmare-associated emotions are limited to fear and anxiety (DSM-IV-TR) or can include all dysphoric emotions, such as anger or despair (ICSD-II). Secondly, only the DSM-IV-TR specifies a criterion that the nightmare or resulting sleep disturbance is associated with significant distress or impairment in waking functioning.

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^a Department of Psychiatry, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15213, USA

^b Department of Psychiatry, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Room E-1124, Pittsburgh, PA 15213, USA

* Corresponding author.

E-mail address: germaina@upmc.edu (A. Germain).

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The expansion of nightmare-associated emotions beyond fear and anxiety is well recognized in the literature, although fear is the most commonly reported emotion in nightmares.³ In contrast, the absence of a distress criterion in the ICSD-II has been criticized, because of evidence that distress is more important than frequency in determining whether nightmares are associated with negative outcomes, including sleep disturbance, psychopathology, or health behavior problems.⁴

The awakening criterion has stimulated significant controversy in the field. Historically, distressing dreams that do not lead to an immediate awakening (at least one that is remembered by the dreamer) have been labeled as bad dreams.⁵ Theorists have suggested that dreaming serves an extinction function, and that the awakenings associated with nightmares, but not bad dreams, disrupts this extinction process.^{4,6} Consequently, many studies dichotomize nightmares and bad dreams as distinct phenomena. However, evidence concerning the importance of awakening to associated distress or psychopathology remains mixed and raises questions about the clinical usefulness of this distinction. Specifically, available treatments to reduce unpleasant dreams usually focus on the extinction of distressing content, rather than on the extinction of these associated awakenings.

Some have argued that all dysphoric dreams fall on a continuum; in this view, nightmares are more intense than bad dreams, both being versions of the same basic phenomenon. Others support the view that the distinction between nightmares and bad dreams relates to underlying differences in the intensity of the emotional content.⁷ However, findings from studies that have investigated differences in dream content intensity between nightmares and bad dreams show small differences between the 2 phenomena. For example, Blagrove and Haywood⁸ reported that dreams judged to have caused awakenings were rated as more unpleasant (in line with nightmares as more intense versions of bad dreams). However, the statistically significant differences in emotion intensity ratings were less than 0.3 on a 7-point scale. A similarly small difference (approximately 0.7 on a 9-point scale) in ratings of emotional intensity in nightmares compared with bad dreams was also reported by Zadra and colleagues.⁹ These small differences in dream intensity between nightmares and bad dreams suggest that dream intensity may not be the primary mechanism that distinguishes nightmares from bad dreams.

The reliability of patients' nocturnal awakening memories is another important, though minimally

considered, aspect of the awakening criterion's clinical significance in defining nightmares. It is possible that bad dreams lead to much shorter awakenings, leading to amnesia of the arousal. For instance, awakenings less than 3 minutes in duration are often associated with retrograde and anterograde amnesia.¹⁰ Blagrove and Haywood⁸ attempted to address this concern by assessing the dreamers' subjective certainty about whether their disturbing dreams woke them up, and they found that participants were generally confident making this decision and particularly so when dreams were very unpleasant. Nevertheless, the lack of objective measures to accurately evaluate the duration of these awakenings makes it difficult to ascertain that bad dreams associated with an awakening are less subject to memory biases.

As indicated earlier, there is divergence between the diagnostic classifications of nightmare distress. Some have argued that nightmare-related distress is more clinically relevant than nightmare frequency to daytime functioning and psychopathology.⁴ From this perspective, nightmares are viewed as a manifestation of the cross-state continuity of distress from waking to sleeping. In support of this assertion, distress is only weakly related to nightmare frequency,¹¹ but it may be more robustly associated with sleep disturbance¹² and measures of psychopathology^{13,14} than with frequency. However, assessments of nightmare distress are vastly underrepresented in the literature,⁴ being limited to 1 validated scale, the Nightmare Distress Scale,¹¹ which may potentially confound nightmare distress with nightmare frequency.¹⁵ Again, longitudinal studies with reliable frequency and distress measures are necessary to fully evaluate the clinical significance of nightmare distress.

Neither classification system includes a criterion for the duration of the nightmare problem, perhaps because the cause of distressing nightmares is often undetermined, or because the clinical meaningfulness of duration of the nightmare problem has not yet been assessed empirically.

Nightmares should not be confused with other distressing nocturnal phenomena. Nightmares are most readily distinguished from other similarly distressing nocturnal events by the extent of mental content, the confusion or disorientation upon awakening, and the presence or absence of memory of the event on the following morning. Sleep recordings show that these distressing nocturnal episodes generally occur in different sleep stages. The particular treatments that are effective for each category of event also vary.

Sleep terrors are associated with intense autonomic arousal. They can begin with a piercing

scream, but they are paradoxically associated with difficulty in awakening the sleeper from the episode and in the sleeper returning to deep sleep after the episode.² In contrast, there is little confusion or disorientation upon awakening from nightmares, and episodes are vividly recalled the following morning. For sleep terrors, if the sleeper has any recall of the event, recollections the next morning are, at best, vague or fragmented descriptions of frightening images.¹⁶ Although nightmares primarily originate in rapid eye movement (REM) sleep, sleep terrors occur in non-REM sleep, specifically the slow-wave sleep of stages 3 and 4.

In contrast to nightmares and sleep terrors, nocturnal panic attacks often occur in the first few hours of the night during the transition from light (stage 2) sleep to deep (stage 3) sleep. Intense arousal is inherent in nocturnal panic attacks, leading to abrupt and complete awakening from sleep in a state of panic, without an obvious trigger and usually without screaming; the panic attacks are associated with a difficulty in returning to sleep.¹⁷ Complicating differential diagnosis is the co-occurrence that has been documented between these parasomnias, such as an association between monthly nightmares and an increased incidence of night terrors.¹⁹ Although sleep terrors and nocturnal panic attacks share a common predisposing condition—sleep deprivation leads to an increased incidence of both^{17,18}—the existing evidence suggests that nightmares lead to sleep disturbance rather than the reverse (see later discussion on association with sleep disturbance).

PREVALENCE AND FREQUENCY

Nightmares are most prevalent during childhood and young adulthood and decline thereafter.⁴ However, prevalence estimates in the general population in all age ranges vary and overlap substantially. From childhood through to early adolescence, between 5% and 50% of children have nightmares, with the prevalence of nightmare “problems” generally falling into the 20% to 40% range. In comparison, up to 85% of adults report at least 1 nightmare within the previous year, 8% to 29% report monthly nightmares, and 2% to 6% report weekly nightmares.^{19–21} The estimates of weekly prevalence of nightmares have proved consistent across cultures.^{12,20–22} Similarly robust are findings of a lower prevalence of nightmares among the elderly, who report at levels 20% to 50% of that of young adults.^{23–25}

The variability in estimates is due, in part, to differences in the criteria used, the definition of

nightmares, the time frame of assessments, the emphasis on distress or nightmares as a “problem” across studies, and the type of informants (eg, patients, primary care physicians, parents). In studies of children, the information, generally gathered from mothers, may show underestimation in the prevalence of nightmares and may be confounded by the occurrence of other common childhood parasomnias, such as sleep terrors. Nightmare prevalence estimates are derived nearly entirely from cross-sectional data.

Sex differences in nightmare prevalence are one of the most consistent findings in the literature,²⁶ with a higher percentage of women reporting nightmares; unacknowledged exceptions do exist.²⁷ Researchers have offered various explanations that are not mutually exclusive for this difference: (1) self-report biases in women, (2) greater vulnerability to risk factors including abuse in women, (3) anxiety and mood disorders in women, (4) sex differences in coping styles, and (5) biologic differences in emotion processing.^{4,11,28–30} Together, these findings highlight the need for conducting longitudinal studies using established diagnostic definitions, an important future step to establishing prevalence rates over the life span. Longitudinal studies would also provide new information on the potential modulators (eg, sex, coping styles, biologic factors) that may contribute to enhanced vulnerability or resilience to chronic nightmares. Although the developmental trajectory remains to be clarified, all estimates to date indicate that nightmares are a prevalent problem, underscoring the need for appropriate clinical identification, assessment, and treatment.

Data concerning the frequency of nightmares are also characterized by substantial variability, mostly because of differences in the assessment methods used across studies. Common methods to assess nightmare frequency are prospective nightmare logs or retrospective estimates of the number of nightmares that occurred over a predetermined period of time (usually 1 month to 1 year). Daily dream/nightmare logs that are completed on awakening in the morning can be a simple checklist or a more extensive dream diary used to record nightmare narratives.

Numerous studies have assessed nightmare frequency, using retrospective or prospective measures. The differences between retrospective and prospective methods affect frequency estimates. Specifically, retrospective estimates have yielded frequency estimates ranging from less than once per year to once per month,²⁷ whereas prospective measures have consistently provided

higher nightmare frequency estimates, particularly when compared with 1-year retrospective nightmare frequency measures.²⁷ Studies that have compared both assessment methods have reported that retrospective questionnaires underestimate nightmare frequency by a factor of 2.5 to 10.^{7,13,31} Many of these studies have been conducted with undergraduates who are in their first semester of college, a time of social and emotional upheaval for many. The latter method may provide overestimates of nightmare frequency in noncollege populations. Differences in frequency estimates that are derived from retrospective and prospective measures are generally interpreted as indicating that retrospective measures underestimate nightmare prevalence. Monitoring of nightmares could potentially increase or decrease their frequency. Nevertheless, prospective nightmare measures have been recommended as the gold standard.^{4,27}

The most sophisticated study on the topic evaluated the comparability of frequency estimates for nightmares and bad dreams, when assessed by 1-year and 1-month retrospective measures and by narrative and checklist prospective measures.²⁸ Including both types of prospective measures was intended to address the question of whether intensive monitoring (with narrative logs) results in higher frequencies than a less demanding approach (using checklist logs). In contrast to predictions, narrative logs produced lower nightmare frequency estimates than checklist logs that did not significantly differ from the 1-month retrospective measure and were possibly higher than the 1-year retrospective measure. When examining bad dreams, both prospective measures produced higher estimates than the retrospective measures, but the prospective and retrospective estimates for bad dreams were not significantly different from one another.

Attempts to assess nightmares via polysomnographic (PSG) recordings in the laboratory have been difficult, because nightmares tend to occur less frequently under these conditions.³² Even posttraumatic nightmares (see the etiology section) have a low incidence (1%–10% vs up to 85% of nights) in the sleep laboratory relative to naturalistic conditions.^{33,34} A pilot study, using ambulatory PSG recording, suggested that the presence of the PSG, rather than the setting, is the crucial factor in the lower observed frequency. In a sample of 12 inpatients in a psychiatric clinic, Spoomaker and colleagues (unpublished data, 2004) found a significantly lower nightmare incidence (8% vs 34.5%) using ambulatory PSG over two 24-hour recordings compared with daily

logs over 7 days. However, the generalizability of this study outside of inpatient settings is uncertain, and PSG studies of nightmares remain too few to draw firm conclusions.

ETIOLOGY

Nightmares are associated with a range of psychiatric symptoms, full-blown psychiatric disorders such as posttraumatic stress disorder (PTSD), and sleep disturbances. Although some psychiatric, personality, sleep, and biologic correlates of nightmares have been described, most extant studies are cross-sectional, precluding conclusive determination of causality and etiology. Although longitudinal studies are awaited, findings suggest that traumatic events, waking psychological distress, or sleep disturbance may contribute to the onset and maintenance of nightmares. Some theories that have been offered on the etiology of nightmares are briefly summarized in the following sections.

Idiopathic Versus Posttraumatic Nightmares

An important etiologic distinction made to date is the difference between idiopathic and posttraumatic nightmares. Idiopathic nightmares refer to nightmares with unknown cause that are unrelated to a specific traumatic event or PTSD. Posttraumatic nightmares refer to dreaming disturbances that are part of the stress reaction following exposure to a traumatic event, either during the acute stress response or over the course of PTSD. Nightmares are a core feature of PTSD, with up to 90% of individuals with PTSD reporting disturbing dreams with some degree of resemblance to the actual traumatic event. Nightmares may occur as frequently as 6 nights a week in individuals with PTSD,³⁵ and they may continue for up to 40 to 50 years after the original trauma.^{36,37}

The distinction between idiopathic and posttraumatic nightmares has not been firmly established in most of the literature available to date. Given the emerging evidence that persistent nightmares in the wake of a traumatic incident predict later posttraumatic symptoms,³⁸ making a differential diagnosis may be particularly important for early intervention to ward off PTSD. In addition, these 2 types of nightmares may differ in their associated sleep disturbance (see the following section on associated features) and in the timing of their occurrence during the sleep period. Further research is necessary to characterize fully the etiology, phenomenology, trajectory, and functional consequences of these ostensibly different categories of nightmares.

Nightmares Due to Thin Psychological Boundaries?

Hartmann and colleagues^{39,40} proposed the constructs of “thin” and “thick” psychological boundaries to characterize chronic (idiopathic) nightmare sufferers versus those with little or no nightmare experience. Frequent nightmare sufferers tend to be more emotionally sensitive, open, and reactive to elements of their internal and external environments. Individuals with no nightmares, on the other hand, tend to be less reactive to internal and external influences. Several subsequent studies have reported positive findings on the relationship between clinical features of schizophrenia-spectrum disorders and nightmare frequency.^{41,42}

Disturbance in a Generally Adaptive Process?

A prevailing assumption is that dreaming is adaptive,⁴³ and thus nightmares may constitute an anomaly in the adaptive process, also described as “a failed dream.”⁴³ However, the evidence in support of this hypothesis is scant. Flanagan⁴⁴ suggested that sleeping, not dreaming per se, is an adaptive process. In contrast, it has also been suggested that nightmares themselves might be the adaptive process. For example, Picchioni and colleagues⁴⁵ reported that nightmares are positively associated with waking attempts to cope with stress, suggesting that nightmares may serve a beneficial function. However, the absence of a direct assessment of successful outcomes of coping in this study makes it difficult, at best, to relate nightmares to functional outcomes. The potential specific role of nightmares in adapting to waking stressors and the specific conditions and mechanisms that contribute to successful or unsuccessful adaptation to stress through dreaming disturbances remain to be investigated.

Genetic Predisposition to Nightmares?

A single study has investigated the possible genetic contributions to nightmares. Using data from the Finnish Twin Cohort study, a nationwide questionnaire study that included 1298 monozygotic and 2419 dizygotic twins aged 33 to 60 years, Hublin and colleagues⁴⁶ found a genetic influence on nightmares that differed slightly between childhood and adult nightmares. Genetic effects accounted for an estimated 45% of the phenotypic variance in childhood and for an estimated 37% in adulthood. The odds ratios for associated psychiatric disorders also varied by age group; children most frequently experiencing nightmares were 3.67 times more likely to have

a psychiatric disorder than those who never experienced nightmares, whereas adults with frequent nightmares had an odds ratio of 5.87. This suggests that nightmares during adulthood have a strong association with psychopathology. Again, these findings highlight the need for longitudinal studies to rigorously assess the moderators and predictors of the trajectory of nightmares and their clinical outcomes over time.

ASSOCIATED FEATURES

Nightmares are associated with sleep disturbance, but longitudinal studies are required to ascertain the directionality of this association. Sleep disruption as a consequence of nightmares is implicit in their definition, given the criterion of awakening to a fully conscious state. Empirical data bear this out, because frequent nightmares are associated with increased reports of sleep-onset and sleep-maintenance insomnia, more frequent nocturnal awakenings, and worse sleep quality.^{21,26,47} Breathing problems (eg, asthma) and snoring are linked to idiopathic nightmares,⁴⁸ whereas an association with full-blown sleep apnea has been reported in posttraumatic nightmares.⁴⁹ Although longitudinal data are limited, 1 prospective study found that posttraumatic nightmares occurring 3 months after a motor vehicle accident were associated with current sleep-onset and sleep-maintenance problems and predicted sleep maintenance difficulties after 1 year.⁵⁰

Objective indices of sleep disruption, as measured by PSG, suggest that idiopathic and posttraumatic nightmares have been associated with different effects on sleep. Although both nightmare types share an association with elevated numbers of periodic limb movements, posttraumatic nightmares are related to longer and more frequent awakenings⁵¹ this relationship is a possible consequence of a lowered arousal threshold during sleep in PTSD,⁵² although the evidence on this is mixed.⁵³ In addition, posttraumatic nightmares may occur earlier in the night than idiopathic nightmares,⁵⁴ but this was not replicated in a recent study.⁵¹ Individuals with idiopathic and posttraumatic nightmares also did not differ on total sleeping time, sleep onset latency, slow-wave sleep, number of microarousals, or any of several REM-related parameters.⁵¹

Waking Disturbance and Psychopathology

Perhaps most relevant to clinical discussions of nightmares is their relationship to waking disturbance or psychopathology. In general, nightmares appear to be linked to a greater incidence of

mental complaints in healthy and clinical populations.

An important part of the nightmare literature has focused on the relationships between personality traits and nightmare frequency. The association between nightmares and anxiety has been most widely investigated. Modest associations between different measures of trait and state anxiety (eg, death anxiety scales, ego strength scales, manifest anxiety scales, and nightmare frequency assessed retrospectively) have been reported.^{7,31,55-60} However, the association between nightmare frequency and anxiety is weakened when assessed with daily nightmare logs instead of retrospective questionnaires.^{7,31} Nightmare-related distress, rather than nightmare frequency, seems to be more strongly related to anxiety.^{13,14,31} In general, studies have consistently reported mild-to-moderate correlations between nightmare frequency and distress and general symptoms of anxiety, mood, somatization, and hostility.^{7,13}

As mentioned previously, nightmares are a core feature of PTSD and may be implicated in the pathophysiology of the disorder. In addition, a pretrauma history of nightmares (possibly idiopathic nightmares) predicts the severity of PTSD.⁶¹ PTSD-related nightmares are often resistant to first-line PTSD treatments, but they respond well to pharmacologic and cognitive-behavioral treatments (see the following section).

Nightmares have also been linked to suicidality. Cross-sectional studies have demonstrated an association between nightmares and both suicidal ideation^{62,63} and actual suicide attempts⁶³; nightmares were the only sleep variable associated with suicidality in a sample of suicide attempters, after controlling for Axis I disorders (including PTSD) and symptom intensity.⁶⁴ One prospective study found that nightmare frequency, per 1-month retrospective self-reports, was related to the risk of suicide, with a 57% higher risk among those reporting occasional nightmares and a 105% higher risk among those reporting frequent nightmares.⁶⁵ Although all of these studies were statistically controlled for possible confounding factors such as sex, depression, and insomnia, only 1 study was controlled for PTSD.⁶⁵ This is an important limitation because PTSD is also linked to suicidality.⁶⁶

TREATMENTS

Most available pharmacologic and psychological literature on the treatments of nightmares is derived from case reports and clinical trials targeting nightmares occurring in the context of PTSD.⁶⁷

Although very few studies have evaluated the effects of these treatments on nightmares of unspecified causes, there is little evidence suggesting that different outcomes would be observed.

Pharmacologic Treatments of Nightmares

By far, the most common treatments of nightmares involve pharmacotherapy. There have been numerous open-label trials, with various agents for the treatment of nightmares. To date, the most effective of available treatments of PTSD-related nightmares is prazosin. Prazosin is an alpha1-noradrenergic antagonist, which is used nightly and associated with clinically meaningful improvements in nightmares, accompanied by reductions in other sleep disturbances and daytime PTSD symptoms. Placebo-controlled studies of prazosin have consistently reported positive effects on nightmares in military and civilian samples.⁶⁸⁻⁷³ However, nightmares recur with prazosin discontinuation.

Several other pharmacologic approaches have also been used with mixed results. Tricyclic antidepressants and monoamine oxidase inhibitors were among the first agents tested for nightmares because of the suppressant effects on REM sleep, but side effects and contraindications limit their clinical use. Selective serotonin reuptake inhibitors (SSRIs), such as paroxetine, sertraline, and fluoxetine, are Food and Drug Administration (FDA)-approved as first-line recommended PTSD treatments, but their efficacy for nightmares is inconsistent across clinical trials. Trazodone and nefazodone, 2 serotonin-potentiating non-SSRI agents, have been associated with moderate-to-large beneficial effects on nightmares in open-label and controlled trials.⁷⁴⁻⁷⁷

Cyproheptadine, an antihistamine with serotonin receptor antagonist properties, has not been found effective for reducing PTSD-related nightmares in a randomized controlled study.^{78,79} Similarly, guanfacine, an alpha2-adrenergic receptor agonist, was not found to be effective in reducing nightmares in patients with PTSD in 2 randomized controlled trials.^{80,81}

Benzodiazepines are often prescribed to patients with PTSD, possibly as agents to manage sleep disturbances,⁸²⁻⁸⁴ despite lack of evidence as to their effectiveness. Two randomized controlled trials found no support for the efficacy of benzodiazepines as treatment for nightmares in PTSD.^{85,86} Although benzodiazepines can reduce nightmares associated with REM sleep behavior disorder,⁸⁷ their efficacy in alleviating nightmares from other causes is unknown.

Atypical antipsychotic drugs have also been tested in the treatment of PTSD-related nightmares in military veterans with PTSD. Studies conducted with risperidone, olanzapine and quetiapine have yielded mixed results.⁸⁸⁻⁹⁰ Zolpidem (nonbenzodiazepine imidazopyridine⁹¹), gabapentin,⁹² and mirtazapine⁹³ show some promise but await more rigorous evaluation.

Cognitive-behavioral Treatments of Nightmares

Cognitive-behavioral treatments of nightmares have focused on 2 general approaches. The first approach is derived from the literature and treatment methods for anxiety disorders. Specifically, desensitization is implemented with the use of repeated exposure to the fearful nightmare content and with habituation to the emotional response triggered by nightmare imagery. Three controlled studies⁹⁴⁻⁹⁶ have assessed the efficacy of desensitization in reducing nightmare frequency, nightmare intensity, psychological symptoms (eg, anxiety, fear, depression, hostility, and general psychological distress), and sleep complaints. Although desensitization studies did not specify the cause of nightmares in patients enrolled in these trials, all have consistently reported improvements in nightmares and also in sleep disturbances and daytime symptoms of anxiety.⁹⁶ Desensitization studies that used nightmare recording or relaxation⁹⁴ as control treatment conditions also noted posttreatment improvements in nightmares. Improvements in nightmares were also found over the periods of follow-up assessments for patients randomized to the desensitization groups, which ranged from 1 to 7 months after treatment. Together, these studies suggest that desensitization can be an effective treatment for nightmares. The efficacy of desensitization for PTSD nightmares, however, has not yet been evaluated.

The second behavioral approach for the treatment of nightmares is imagery rehearsal therapy (IRT) and its variants. The goal of IRT is to decrease the frequency or intensity of nightmares by (1) repeatedly rehearsing (practicing) new dream scenarios during wakefulness, and (2) revising compensatory cognitions and behaviors that perpetuate nightmares. In comparison to desensitization, IRT does not involve exposure to distressing material. IRT emphasizes rescripting the original nightmare scenarios into new, nondistressing dream scenarios that are then mentally rehearsed several times per day. Exposure to the original nightmare scenarios is discouraged, and repeated sessions of mental rehearsal of new dream scenarios are implemented daily, 1 to 3

times per day. Generally, the instructions on how to create new dream scenarios are minimal. Patients may choose to alter the ending of the dream, to change specific elements of the original content (eg, characters, nature of interpersonal and social interactions), or to create an entirely new dream scenario.

A series of controlled studies showed that rescripting and mentally rehearsing new dream scenarios alone, with limited to no exposure to the distressing dream content or intense emotional reactions, can significantly alleviate idiopathic nightmares and PTSD-related nightmares, in patients reporting at least 1 nightmare per week⁹⁸ and sleep complaints.^{47,98} A large controlled trial, involving sexual assault survivors with trauma-related nightmares, replicated these findings when compared with women assigned to a wait-list control group, by showing clinically meaningful improvements in nightmare frequency, reduced severity of daytime PTSD symptoms, and improved sleep quality.⁹⁹

A variant of IRT, called Exposure, Relaxation, and Rescripting Therapy (ERRT¹⁰⁰), has also been associated with long-term improvements in nightmare frequency, depression-symptom severity, PTSD-symptom severity, and sleep quality for trauma-related nightmares, compared with effects observed in a wait-list control group. ERRT is a combination of (1) education about trauma, PTSD, and sleep; (2) exposure to the nightmare content and distressing themes; (3) diaphragmatic breathing and daily progressive muscle relaxation; and (4) rescripting of the nightmare scenario guided by the therapists and other members of the treatment group. Contrary to IRT, ERRT encourages exposure to the distressing nightmare content. Future research is awaited to determine which patients to treat and how much exposure should be given in the treatment of nightmares.

To date, IRT has shown efficacy with PTSD and non-PTSD related nightmares^{97,98,101,102} in civilian and military samples.^{99,103} However, to fully evaluate and compare the efficacy of different cognitive-behavioral techniques for the treatment of nightmares, more stringent control treatment conditions and direct comparisons between IRT approaches and desensitization or exposure are required.

Other psychological approaches have also been used in the treatment of nightmares. For instance, positive case reports and case series are available in the literature for lucid dreaming,¹⁰⁴ hypnosis,¹⁰⁵ eye movement desensitization and reprocessing,¹⁰⁶ and psychodynamic therapy.^{107,108} These approaches await controlled clinical trials to determine efficacy for nightmares and the related

impact of sleep disturbances and daytime functional impairments and distress.

SUMMARY

Nightmares, a common experience for most of the general population, are even more prevalent and frequent among clinical populations. This increased prevalence is consistent with converging evidence of their potential clinical significance across diagnostic categories. Accumulating evidence links nightmares to waking distress and psychopathology; prospective studies suggest that nightmares may be a risk factor for PTSD and increased suicidality, offering new venues for prevention and interventions.

Methodological limitations and differences, across studies to date, preclude a more complete understanding of many aspects of this fascinating phenomenon. Thus, more rigorous methods are needed to address numerous areas. Firstly, the variability in assessment methods may have led to imprecise prevalence estimates, and this limits our ability to compare findings across studies. Studies of nightmares under controlled laboratory conditions may provide novel insights into the psychophysiological correlates of these nocturnal events; however, multi-night designs, with larger samples studied under ecologically valid conditions, are required to accurately evaluate the frequency and prevalence of nightmares in the general population and in clinical samples. Such studies would also permit assessments of the relationships between nightmare distress and frequency. Secondly, many questions remain regarding the cause and outcomes of nightmares. Most findings concerning nightmares and waking function are limited to correlations based on cross-sectional observational data. Experimental and longitudinal designs are required to address questions around the relationships between nightmares, sleep disturbance, and psychopathology. Even in the case of posttraumatic nightmares, where a clear event precedes the onset of nightmares, little is known about the biopsychosocial pathways through which the trauma exposure affects dreaming. More randomized controlled studies are necessary (1) to evaluate and compare available and promising treatment strategies and (2) to establish guidelines and algorithms to guide clinicians in the treatment of nightmares. Effective nightmare treatments can be used as probes to test specific hypotheses regarding the psychophysiological mechanisms underlying nightmares.

A small contingent of highly dedicated scientists is responsible for the laudable advancements in the nightmare literature to date. These researchers

have also posited some compelling hypotheses that deserve more rigorous testing. Opportunities for novel contributions to and advancement of this important area of clinical investigation await the efforts of the broader research community.

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SLEEP AND DREAMS IN POSTTRAUMATIC STRESS DISORDER

By Anne Germain

Sleep disturbances are a core feature of posttraumatic stress disorder (PTSD). PTSD is characterized by three symptom clusters that arise and persist for more than one month after exposure to a traumatic event, defined as experiencing or witnessing of a real or perceived threat of death or injury to one's self or others, and associated with intense feelings of fear, horror, or hopelessness. The symptom clusters are re-experiencing symptoms, avoidance and hyperarousal.

Nightmares and insomnia are hallmarks of PTSD (Ross et al., 1989). Nightmares refer to replays of traumatic events, but other unpleasant dreams are also common and associated with comparable distress. Insomnia refers to difficulty falling or staying asleep. Other sleep disturbances endorsed by patients with PTSD include bad dreams unrelated to traumatic events, simple and complex motor behaviors, nocturnal panic attacks, and sleep terrors (Germain et al., 2005). Although considered symptoms of stress reactions, sleep disturbances can develop into persistent and independent comorbid conditions, which are often resistant to pharmacological or cognitive-behavioral PTSD treatments.

Findings from animal and human studies support the hypothesis that sleep disturbances play an important role in the development and persistence of PTSD and associated poor health outcomes (Germain et al., 2008). For instance, the occurrence of sleep disturbance after exposure to traumatic events increases the risk for developing chronic PTSD, and sleep disturbances independently contribute to poor clinical outcomes in patients with PTSD. Additionally, clinical observations suggest that the normalization of sleep dis-

turbances may be critical in remission and recovery. Sleep-focused treatments, such as imagery rehearsal for nightmares and prazosin (a noradrenergic alpha-1 antagonist), are associated with clinically meaningful improvements in nighttime and daytime symptoms of PTSD (Maher et al., 2006). However, the study of sleep in PTSD has been mostly limited to cross-sectional studies using self-report or polysomnographic measures (Kobayashi et al., 2007).

Because of the importance of sleep in PTSD and the limitations of extant research, our program at the University of Pittsburgh encompasses two approaches with a primary focus on sleep and PTSD. The first focuses on investigating the role, nature, and neurobiological underpinnings of sleep disturbances that contribute to PTSD. The second focuses on evaluating the efficacy of established and novel sleep-specific pharmacological and cognitive-behavioral interventions on nighttime and daytime symptoms of PTSD, and identifying how response to sleep treatments normalizes the behavioral, psychophysiological, and functional neuroanatomical correlates of PTSD during sleep and wakefulness. Our ongoing clinical and neuroimaging studies focus on

Anne Germain is Assistant Professor of Psychiatry at the University of Pittsburgh School of Medicine Center. She obtained her doctoral degree in Clinical Psychology from the Université de Montréal in 2001, and completed her post-doctoral training at the University of Pittsburgh in 2005. Her research focuses on the assessment, treatment and neurobiological underpinnings on nightmares and insomnia comorbid with stress-related disorders, with emphasis on PTSD. Her research also focuses on identifying the sleep-specific predictors of treatment response.
germaina@upmc.edu

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sleep and PTSD in combat-exposed military veterans. Our studies include a broad array of sleep assessments including validated self-report measures, objective measures of sleep and wakefulness patterns, such as actigraphy (a wristwatch-like device composed of accelerometers to monitor and record activity/movement levels across several 24-hour periods), and in-home or laboratory-based sleep studies (polysomnography), quantitative electroencephalography (qEEG), and positron emission tomography.

Understanding the psychophysiological and neurobiological underpinnings of PTSD across the sleep-wake cycle is essential in developing and refining prevention and intervention strategies to enhance resilience to traumatic stress and to hasten the recovery of patients with PTSD. 